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Altruistic punishment in patients with Parkinson's disease with and without impulsive behaviour

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ABSTRACT

Punishing violators of social norms when there is personal cost is known as altruistic punishment. We tested patients with Parkinson's disease (PD) with and without impulsive–compulsive behaviours (ICBs) and matched control subjects, on and off their regular dopamine replacement therapy on a task, in which the patients decided whether or not to invest a sum of money with a trustee. The sum was then quadrupled and the trustee could decide whether or not to return a portion of the investment. Participants could punish the trustee after they were informed of the trustee's decision. We found that PD patients without ICBs on or off medication punished more often than controls, whereas PD patients with ICBs punished more than controls on medication, but similar to controls off medication. These results suggest a role for dopamine in altruistic punishment decisions in PD patients with impulsive compulsive behaviour.

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1. Introduction

Violation of social norms or unfair behaviour by members of a group induces a desire for society to punish the miscreants (Fehr & Gachter, 2002). Punishing violators of social norms is gratifying, as people are prepared to accept personal loss in order to serve up justice. Punishment when there is personal cost is known as altruistic punishment, and has been shown to reduce the amount of unjust behaviour within groups (Boyd, Gintis, & Bowles, 2010; Fehr & Gachter, 2002; Sigmund, 2007).

A functional imaging study in healthy volunteers has shown that the dorsal striatum, in particular the caudate nucleus is critically involved in mediating punishment and greater activation in the ventral caudate is associated with higher altruistic punishment. This study also indicated that people derive satisfaction from punishing norm violations (de Quervain et al., 2004).

Other fMRI studies have demonstrated that the dorsolateral prefrontal cortex, the insula (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003) and the caudate nucleus (King-Casas et al., 2005) play important roles in processing fair and unfair behaviour. The dorsal-lateral prefrontal cortex and the caudate are directly connected in a frontal–striatal loop (Haber, Kim, Mailly, & Calzavara, 2006), and therefore both regions are likely to be relevant in mediating responses to fair and unfair behaviour.

The dopamine innervation of the dorsal striatum is severely depleted in Parkinson's disease (PD), leading to bradykinesia and rigidity. Dopaminergic replacement is used to correct the depleted dopamine levels and improve motor deficits. Patients with PD are commonly anhedonic (Todes & Lees, 1985), but there is a subgroup of patients who during chronic dopaminergic treatment exhibit a spectrum of biological impulsive compulsive behaviours (ICB) including pathological gambling, hypersexuality, compulsive shopping, binge eating, reckless generosity, punding and the compulsive use of dopaminergic medication (dopamine dysregulation syndrome or DDS) (American Psychiatric Association, 2000; Brewer & Potenza, 2008; Lawrence, Evans, & Lees, 2003; O'Sullivan, Evans, & Lees, 2009; Weintraub & Potenza, 2006). Clinical data suggest that dopamine replacement medication, especially dopamine agonists, directly provoke these compulsive behaviours (Potenza, Voon, & Weintraub, 2007; Voon, Hassan, Zurowski, Duff-Canning, et al., 2006; Weintraub et al., 2006) and a recent study has demonstrated a positive association between impulsivity and altruistic punishment (Crockett, Clark, Liebermann, Tabibnia, & Robbins, in press).

There were several motivations for this study. First, following recent work by our group where we described differences in learning from positive and negative feedback between PD patients with impulsive compulsive behaviors (PD + ICB) and PD patients without impulsive compulsive behaviors (PD) (Djamshidian et al., 2010), we

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hypothesized that PD + ICB patients might be less likely to punish as they might be less sensitive to the aversive aspects of the lack of reciprocation in the trust task. Second, as PD + ICB patients violate social norms themselves, we thought they might be less likely to punish others that violate social norms. Therefore, we tested PD patients with (PD + ICB) and without (PD) impulsive compulsive behaviour on and off medication and compared their results with healthy controls matched for age and education. We further hypothesized that on dopaminergic medication both groups of patients would punish to a greater amount and more frequently than when off medication given the role of the striatum in mediating punishment, and the important role of dopamine in modulating behaviours mediated by the striatum.

2. Patients and methods

Patients were recruited from a database of attendees at the National Hospital for Neurology and Neurosurgery Queen Square, London. All patients fulfilled the Queen Square Brain Bank criteria for the diagnosis of PD (Gibb & Lees, 1988) and were taking L-dopa medication. Controls were usually recruited from amongst the patient's spouses or partners. All participants provided written informed consent to protocols approved by the UCLH Trust local ethics committee. Patients who scored under 27/30 points on the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) were excluded from this study. The study was performed between-groups, such that no patients were tested both off and on: this eliminates the possibility of order effects, which may be more likely with the task used in this study than other studies. Thirteen PD + ICB patients were tested off medication and 14 on medication. Similarly 12 PD patients were tested off medication and 14 on medication. We compared these results with 26 healthy controls. Table 1 includes detailed demographic information on all subjects. All patients were screened for sub-classes of ICBs. Pathological gambling was defined using the DSM IV criteria, compulsive shopping was defined using McElroy's criteria (McElroy, Keck, Pope, Smith, & Strakowski, 1994), hypersexuality was defined as suggested by Voon, Hassan, Zurowski, de Souza, et al. (2006). All patients were additionally screened for punding (Evans et al., 2004).

Patients who were tested "off" performed the test between 8.00 am and 9.00 am prior to their morning medication and had not taken their medication for at least 12 h. Patients who were tested on medication were tested at a similar time of the morning when they felt that their motor symptoms had been well controlled, about 1 h after their usual morning anti-Parkinson medication. The therapeutic motor response to L-dopa was assessed by UPDRS scores (PART 3) during "off" and "on" state. All patients had an excellent L-dopa response. Levodopa equivalent units (LEU—Table 1) were calculated as described previously (Evans et al., 2004). Testing was usually performed in patient's homes or a hotel room using a laptop computer. Distractions were minimized as much as possible.

The task was a computerized trust game (de Quervain et al., 2004) designed to assess altruistic punishment in fair and unfair rounds. Participants were told that they were playing live against 8 human players, but in fact all were playing against the computer. To ensure that the participants believed they were playing against human participants we took several precautions. The tests were administered on a laptop, often in the participant's homes. We therefore used an external modem which initiated a connection to the internet. During this connection process the screen displayed "connecting to the first player" and later on during play "your decision has been sent to your first partner". Random time delays were also used while subjects waited to see if their "partner" would reciprocate.

Participants received an allowance at the start of play and were told that they could start the game by entrusting £10 or nothing to each of the eight trustees, as was done previously (de Quervain et al., 2004). Participants played with one trustee per round. Thus, a single decision at the start of play dictated the amount entrusted by the player in all subsequent rounds. None of the subjects chose not to entrust the £10 at the start of play. Participants were told that each trustee had been given £10 already and that in each round the invested £10 was quadrupled. Thus, each of the 8 players (trustees) received £50 in total. The trustee could either respond in a trustworthy manner and share (send back £25) or could keep all the money (£50). Following this the participants were given an additional £10, and had the option to punish the trustee which would result in a decrease in the amount of money the trustee was left with. However, the participant was informed that they would lose £1 for every £2 they chose to punish the trustee. Their punishment options were £0, £5, £10, £15 and £20, at costs to the participant of £0, £2.50, £5.00, £7.50 and £10. In three of the eight rounds participants were treated in a fair manner (receiving £25 back), in the rest of the rounds they were treated in an unfair manner (receiving £0 back). The researcher made sure that all participants understood the rules. Participants either pressed the necessary computer key by themselves or if more convenient gave verbal commands to the researcher who pressed the keys on their behalf. Participants were given the average outcome across all rounds of play. Within each group, controls received £14, PD + ICB patients off medication £13, PD patients off medication £10 and PD patients on medication from both groups £9 for completing this study, on average.

2.1. Data analysis

Analyses were carried out on the amount that the patients chose to punish in each round. The raw scores were 1 if participants did not punish or respectively 2 = £5, 3 = £10, 4 = £15 and 5 = £20. We carried out analyses using standard linear models and we present these in the results section. For the linear model, a mixed model ANOVA was performed with the scores as the dependent variable. Trials (round 1–8) and valence (fair and unfair) was modelled as within subject factors, with trial nested under valence. We also modelled group (PD off medication, PD on medication, PD + ICB off medication, PD + ICB on medication and Controls) and included subject as a random factor nested under group. Interactions between the fixed effects were also assessed. All post hoc comparisons were Bonferroni corrected.

We carried out a second ANOVA on just the PD and PD + ICB groups to examine explicit medication and group (PD vs. PD + ICB) effects. This model was identical in all other factors to the above model, except the group variable which had 5 levels in the first analysis was split into 2 factors each with 2 levels (as controls were excluded): patient diagnosis (+ICB/−ICB) and medication (on/off dopamine).

As the dependent variable values took on a discrete set of values, we also used a generalized linear model (SPSS) with a multinomial cumulative logit link function to assess significance (results in Appendix A). The cumulative logit maintains the ordinal relation of the responses without making the Gaussian assumption on the residuals. Wald chi-square was used to assess statistical significance. Thus, the

Table 1
Participant demographic information.

	Controls	PD + ICB on med	PD+ ICB off med	PD on med	PD off med	*F*-value except[a]	*p*-Value
Participants (no.)	26	14	13	14	12		
Age (yrs)	58 ± 11	55.0 ± 11.9	56.6 ± 6.4	66.3 ± 8.0	64.2 ± 8.3	3.5	0.01
Gender (male)	15	11	9	12	10	$\chi^2 = 5.1$[a]	0.28
At disease onset	–	44 ± 10.5	49 ± 7.6	54.1 ± 9.5	53.1 ± 8.8	3.5	0.023
Disease duration (yrs)	–	11.3 ± 5.2	7.7 ± 4.7	12.2 ± 7	11.1 ± 6.9	1.45	0.24
Education (yrs)	13.5 ± 3.0	12.3 ± 2.3	14.7 ± 3.5	14.0 ± 4.3	15.2 ± 4.0	1.54	0.2
LEU dose (mg/day)	–	858 ± 348	801 ± 479	812 ± 346	825 ± 378	0.05	0.98
L-dopa (mg/day)	–	692.9 ± 281	521 ± 227	604 ± 315	466 ± 247	1.6	0.19
DA (patients)	–	8	9	10	9	$\chi^2 = 1.8$[a]	0.6
UPDRS on	–	19.4 ± 8.0	14.1 ± 5.2	17.7 ± 10.9	12.5 ± 4.0	1.8	0.16
UPDRS off	–	36.8 ± 15.4	29.2 ± 11.1	27.7 ± 9.5	24.0 ± 7.0	2.3	0.09
Average change in UPDRS (%)		46	52	36	48		
Active ICB at time of testing	–	8	8	–	–		NS
Gambling	–	4	3	–	–		NS
Hypersexuality	–	6	8	–	–		NS
Shopping	–	6	8	–	–		NS
Punding	–	2	2	–	–		NS
Kleptomania	–	1	–	–	–		NS

UPDRS = Unified Parkinson's Disease Rating Scale; LEU = L-dopa equivalent units; DA = dopamine agonists. All values are mean ± s.e.m. NS = not significant.

[a] Chi-square.

punishments were modelled discretely, but the order of the punishment values was maintained such that 2 was modelled as greater than 1, 3 greater than 2 and 1, etc. The results were closely replicated (see Appendix A). ANOVA models are known to be robust to violations of distribution assumptions.

3. Results

Groups were generally well matched demographically. However, we found a significant effect of age between the 5 groups ($F_{4,74} = 3.5$, $p = 0.01$; controls, PD on, PD off, PD + ICB on and PD + ICB off). Post hoc analysis revealed that the PD on group was older than the PD + ICB on ($p = 0.03$) but not the PD + ICB off group ($p = 0.12$). There was no difference between the control and the PD on group ($p = 0.13$), no difference between the PD off and the PD + ICB on group ($p = 0.2$) and all other patients groups ($p > 0.57$). There was also a significant effect of age of onset ($F_{3,49} = 3.4$, $p = 0.03$). Post hoc analysis showed that the PD + ICB on group had an earlier disease onset ($p = 0.03$) than the PD on group, consistent with previous studies (Voon et al., 2007; Weintraub & Potenza, 2006). There was no difference in age of disease onset between the PD + ICB on group and the PD off group ($p = 0.08$) nor between the other groups ($p > 0.92$). There was also no difference in the LEU dose ($F_{3,48} = 0.05$, $p = 0.98$) or the daily L-dopa dose ($F_{3,48} = 1.6$, $p = 0.19$).

3.1. Analysis of punishment behaviour

We carried out an ANOVA with dependent variable the amount of punishment (Fig. 1), with group entered as five levels (PD on, PD off, ICB on, ICB off, controls). We found significant main effects of group ($F_{4,73} = 11.17$, $p < 0.001$) and valence ($F_{1,73} = 265.83$, $p < 0.01$), where valence was fair vs. unfair outcome. There was also a significant interaction between group and valence ($F_{4,73} = 4.54$, $p = 0.002$). Given the interaction with valence, we ran separate ANOVAs on the fair and unfair rounds. In the fair rounds there was no effect of group ($F_{4,73} = 1.95$, $p = 0.111$). In the unfair rounds there was a main effect of group ($F_{4,73} = 9.24$, $p < 0.001$).

Next we compared the PD and ICB groups to directly examine a diagnosis of ICB as well as the effects of medication. Thus, group was split by ICB diagnosis (+ICB/−ICB) and medication (on/off dopamine replacement). The main effect of group just missed significance ($F_{1,48} = 3.71$, $p = 0.060$). There was, however, a significant main effect of medication ($F_{1,48} = 5.76$, $p = 0.020$) and a significant interaction between group and medication ($F_{1,48} = 7.68$, $p = 0.008$). There was also a valence by group interaction ($F_{1,336} = 4.97$, $p = 0.026$) and a significant valence by group by medication interaction ($F_{1,336} = 9.71$, $p = 0.002$). As there was a difference in age between groups, we also carried out an analysis where we covaried out the effect of age. Adding age as a covariate, however, did not affect significance of any parameters. Given the interactions with valence, we next split this ANOVA by valence and ran separate ANOVAs. In the fair rounds there was no effect of group ($F_{1,48} = 0.04$, $p = 0.852$) or medication ($F_{1,48} = 1.2$, $p = 0.279$). In the unfair rounds, however, there was a main effect of group ($F_{1,48} = 4.05$, $p = 0.050$), an interaction between group and medication such that PD on and off punished strongly, whereas PD + ICB on also punished strongly, but PD + ICB off punished less ($F_{1,48} = 8.24$, $p = 0.006$). The main effect of medication just missed significance ($F_{1,48} = 3.96$, $p = 0.052$).

Following this we carried out pair-wise post hoc comparisons between all five groups in just the unfair rounds (Bonferroni corrected). This analysis showed that PD on, PD off and PD + ICB on punished significantly more than controls ($p < 0.01$) whereas the PD + ICB off group punished similarly to controls ($p = 1.000$). Furthermore PD on and PD + ICB on punished significantly more than the PD + ICB off group ($p < 0.05$), but PD off only reached trend level vs. the PD + ICB off group ($p = 0.067$).

As dopamine loss in PD progresses over the course of the disease we were interested in whether there would be any correlations between disease duration and the amount of punishment. Therefore, we carried out correlations between disease duration and the amount of punishment in the unfair condition, but found no significant effects ($p > 0.345$). There was also no correlation between UPDRS scores and punishment ($p > 0.405$).

4. Discussion

We have demonstrated increased altruistic punishment behaviour in PD + ICB patients on dopaminergic medication compared to controls. These patients behaved similarly to controls off medication, whereas PD patients without impulse control behaviours punished more than controls whether they were medicated or not. The decision to punish is likely influenced by the participant's response to the amount returned by the trustee. When the trustee reciprocates, the investor makes money on the transaction, and when the trustee withholds the investor loses money. Winning and losing money engage learning processes in non-social contexts, and extensive studies have shown that dopamine levels in PD are related to learning from non-social positive and negative feedback (Bodi et al., 2009; Cools, Barker, Sahakian, & Robbins, 2001; Djamshidian et al., 2010; Frank, Seeberger, & O'Reilly, 2004; Rutledge et al., 2009). Additionally, many subjects may be unwilling to punish trustees, even if they have a strong negative affective response to the lack of reciprocation, whereas others may punish even though they feel little resentment.

We found that PD + ICB patients off medication punished to the same degree as controls, whereas the PD + ICB group on medication punished more. Thus, even though dopamine medication can lead to the development of ICBs, and ICBs are inconsistent with social norms, PD + ICB patients enforce social norms more strongly on than off medication. A reduction in sensitivity to negative feedback in PD + ICB patients off medication has been shown in some (Djamshidian et al., 2010) but not all studies (Voon et al., 2010). It

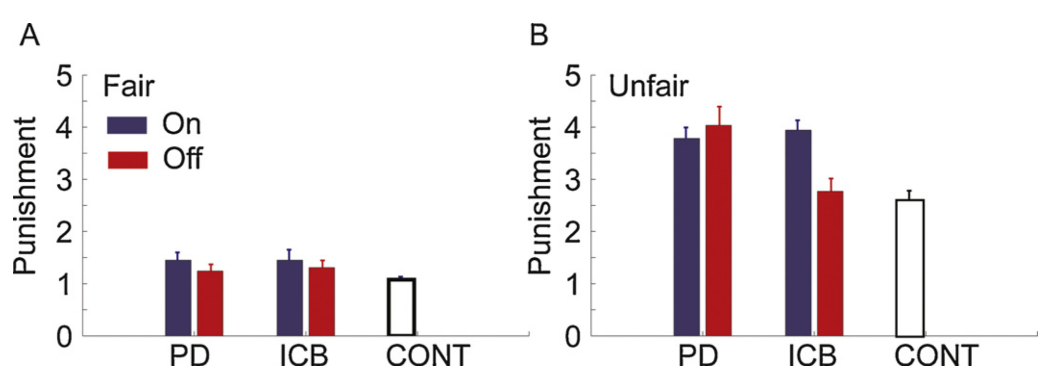

Fig. 1. Average punishment score of participants in fair and unfair rounds. Error bars are ±1 s.e.m.

is possible, therefore, that the PD + ICB off group may punish less than all the other patient groups because they are less sensitive to the lack of reciprocation by the trustee. Additionally, dopaminergic medication has been shown to increase impulsive choice in PD + ICB patients (Voon et al., 2009) and impulsivity correlates positively with altruistic punishment in *The Ultimatum Game* (Crockett et al., in press). Increased punishment in the PD + ICB group on medication could, therefore, be due to sensitivity to negative feedback and increased impulsivity.

The PD group without impulse control disorders punished more than controls both on and off medication. When the PD group was compared to the PD + ICB group, there was an interaction between medication status and group, and the difference between PD off and PD + ICB off just failed to reach significance. Interactions between medication and group have already been observed across a range of behaviours including impulsive choice (Voon et al., 2009), learning (Djamshidian et al., 2010; Voon et al., 2010), risk proneness (Djamshidian et al., 2010), affective states and reward responsivity (Evans, Lawrence, Cresswell, Katzenschlager, & Lees, 2010). In our study, only the PD + ICB patients were sensitive to behavioural changes induced by their dopaminergic medications. This is consistent with the observation that clinically impulsive behaviour arises due to medication in the PD + ICB group, but not in the normal PD group (Voon et al., 2009).

There are also differences in the pre-morbid personalities of PD and PD + ICB patients. PD patients have a lower premorbid risk of smoking, and tend to be anhedonic, moralistic, punctual, risk averse and altruistic with a strong adherence to social norms (Evans et al., 2006; Ishihara & Bayne, 2006; Menza, 2000; Prick, 1966; Todes & Lees, 1985). Recent studies have suggested that some of these behaviours may be related to the prefrontal cortex (Abe et al., 2009). In contrast PD patients who develop ICBs are higher novelty seekers with an increased premorbid incidence of illicit drug or alcohol addiction (Lim, Evans, & Miyasaki, 2008; Potenza et al., 2007). The PD group therefore may punish more than the ICB group off medication, due to their inherent personality traits. The exact neurobiological mechanisms that underlie these personality and task behavioural differences are not yet clear, however.

Brain imaging studies using a similar task have shown that the medial caudate nucleus is activated during punishment, and a ventral caudate focus correlates with the amount of punishment (de Quervain et al., 2004). The desire to punish altruistically appears to be driven by negative emotions brought about by the fact that trustees fall short of social norms when they do not reciprocate (Fehr & Gachter, 2002). However it is unclear whether punishment in the patient groups is only driven by altruism or whether other factors such as aggression have to be taken into account. Clinically PD + ICB patients can become quite aggressive and do not have insight that their behaviours are unacceptable to others. This would mean that punishing or criticizing PD + ICB patients for bad behaviour off medication would not be effective since they do not recognize norm violations which might contribute to the patient's low insight.

Further behavioural studies which include self rating questionnaires to tap the motivation of altruistic punishment are required to clarify our findings.

5. Conclusion

We have found that PD patients with ICBs respond differently than normal PD patients in a trust game in which patients can deliver punishment altruistically. Both groups of medicated patients punished more than controls, but off medication the PD group still punished more than controls, whereas there was no difference between the PD + ICB cases and healthy controls. Unravelling the factors that lead to these differences will provide important insight into impulse control behaviours, as well as the neural, pharmacological and anatomical mechanisms that underlie these tasks.

Conflict of interest

All authors reported no conflict of interest in the content of this paper. AJL receives honoraria from Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion, grants from the PSP Association, Weston Trust—The Reta Lila Howard Foundation and consultancies from Genus. SOS has received honoraria from Britannia Pharmaceuticals. BBA receives research support from Wellcome, and the Intramural research program of the National Institute of Mental Health.

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Appendix A. Results of generalized linear model

Under the generalized linear model, with group entered as five levels (PD on, PD off, ICB on, ICB off, controls). We found significant main effects of group (Wald $\chi^2 = 15.76$, $p = 0.003$) and valence (Wald $\chi^2 = 224.43$, $p < 0.001$) and a significant interaction between group and valence (Wald $\chi^2 = 10.20$, $p = 0.037$).

When we compared the PD and ICB groups on and off medication, the main effect of group was not significant (Wald $\chi^2 = 1.70$, $p = 0.192$). There was, however, a significant main effect of medication (Wald $\chi^2 = 8.38$, $p = 0.004$) and a significant interaction between group and medication (Wald $\chi^2 = 4.54$, $p = 0.033$). There was also a valence by group interaction (Wald $\chi^2 = 4.39$, $p = 0.036$) and a significant valence by group by medication interaction (Wald $\chi^2 = 6.23$, $p = 0.044$).

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